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By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

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PRIORITY DOCUMENT

SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

07-17-02

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR §1.53(c).

Express Mail No. EL 904265538US	Docket No. 02-420-A	Type a plus sign (+) inside this box:	+

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TITLE OF THE INVENTION (280 character maximum)

Ephrin Receptor Inhibitors and Methods of Use

CUSTOMER NUMBER

20306
PATENT TRADEMARK OFFICE

McDonnell Boehnen Hulbert & Berghoff

ENCLOSED APPLICATION PARTS (check all that apply)

☒ Specification Number of Pages 20 ☐ Drawings Number of Sheets

☒ Other: Postcard

METHOD OF PAYMENT FOR THIS PROVISIONAL APPLICATION FOR PATENT

☐ Applicant claims small entity status. See 37 CFR 1.27 ☒ A check or money order is enclosed to cover the Provisional Filing Fee. ☒ The Commissioner is hereby authorized to charge filing fees and credit Deposit Account Number: 13-2490.	PROVISIONAL APPLICATION FOR PATENT FILING FEE AMOUNT ($)	$160.00

CERTIFICATE OF MAILING

I hereby certify that, under 37 CFR § 1.10, I directed that the correspondence identified above be deposited with the United States Postal Service as "Express Mail Post Office to Addressee," addressed to the Asst. Commissioner for Patents, Box Patent Application, Washington, DC 20231, on the date indicated below.

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.
X No _____ Yes, the name of the U.S. Government agency and the Government contract number are _____

Respectfully submitted,

SIGNATURE: Brad Crawford

Date: July 15, 2002

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Application Information

Title Line One::	Ephrin Receptor Inhibitors and Methods of Use
Title Line Two::	
Total Drawing Sheets::	0
Formal Drawings?::	No
Application Type::	Provisional
Docket Number::	02-420-A

Representative Information

Representative Customer Number	020306

[redacted]

EPHRIN RECEPTOR INHIBITORS AND METHODS OF USE

BACKGROUND OF THE INVENTION

Field of the Invention

[0001] The present invention is in the field of inhibitors of the ephrin receptor kinase and methods of their use for inhibition and treatment of diseases mediated, at least in part, by ehprin receptor kinases.

Summary of the Related Art

[0002] Receptor tyrosine kinases (RTK's) and their ligands play a critical role in cell proliferation, survival, mitogenesis and differentiation. The deregulation of RTK's can lead to uncontrolled cell growth sometimes resulting in a transformed malignant phenotype. RTK's are attractive targets for small molecule oncology drug discovery since inhibition of EGF, VEGF and ephrin signal transduction will prevent cell proliferation and angiogenesis, two key cellular processes needed for tumor growth and survival (Matter A. Drug Disc Technol 2001 6, 1005-1024). EGF and VEGF receptors are previously described targets for small molecule inhibition.

[0003] Overexpression of Eph receptors has been linked to increased cell proliferation in a variety of tumors (Zhou R 1998 Pharmacol Ther. 77, 151-181; Kiyokawa E, Takai S, Tanaka M et al 1994 Cancer Res 54, 3645-3650; Takai N Miyazaki T, Fujisawa K, Nasu K and Miyakawa. 2001 Oncology reports 8, 567-573).

[0004] The family of Eph receptor tyrosine kinases and their ephrin ligands play important roles in a variety of processes during embryonic development and also play a role in pathological angiogensis. The Eph receptors comprise the largest family of receptor tyrosine kinases and are divided into two groups, EphA and EphB, based on their sequence homology. The ligands for the Eph receptors are the ephrins which are membrane anchored. Ephrin A ligands bind preferentially to EphA receptors whilst ephrin B ligands bind to EphB receptors. Binding of ephrins to Eph receptors causes receptor autophosphorylation and typically requires a cell-cell interaction since both receptor and ligand are membrane bound.

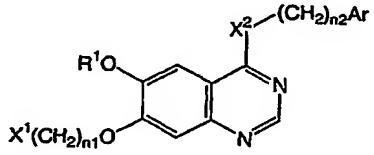
SUMMARY OF THE INVENTION

[0005] The present invention comprises quinazoline-based compounds that are ephrin inhibitors, pharmaceutical compositions comprising the compounds, and methods of using the compounds and

compositions to inhibit ephrin receptors and treat diseases mediated by ephrin receptors, including diseases associated with abnormal cell proliferation (e.g., tumors) and angiogenesis.

DETAILED DESCRIPTION OF THE INVENTION

[0006] In a first aspect, the invention comprises ephrin tyrosine kinase inhibitors of structural formula I:



I

and pharmaceutically acceptable salts, esters, amides, and prodrugs thereof wherein

X^1 is Y^1-Z^1-;

Z^1 is an unsaturated or mono- or poly-unsaturated C_3-C_{14}-mono- or fused poly-cyclic hydrocarbyl optionally containing one, two, or three annular heteroatoms per ring and optionally substituted with from 1 to 3 R^{50} substituents;

Y^1 is -H, C_1-C_6-alkyl-L^2-L^1- optionally substituted by R^{50}, $X^3(CH_2)_{n3}$-, or $R^2R^3N(CH_2)_{n4}$-

X^3 is a saturated 5-7 membered heterocyclyl containing one or two annular heteroatoms and optionally substituted with from 1 to 3 R^{50} substituents;

L^1 is -CO-, or -SO_2-;

L^2 is a direct bond, -O-, or -NH-;

n1, n3, and n4 are independently 0, 1, 2, or 3;

R^2 and R^3 are independently C_1-C_3-alkyl optionally substituted with from 1 to 3 R^{50} substituents;

R^1 is C_1-C_3-alkyl optionally substituted with from 1 to 3 R^{50} substituents;

X^2 is -O-, -S-, or –NH-;

Ar is aryl with 1 to 3 ring substituents selected independently from Me-, -F, -Cl, -Br, -OH, -OMe;

n2 is 0 or 1;

R^{50} is halo, -OH, -$NR^{51}R^{52}$, -SH, -CO_2H, -CN, -NO_2, -SO_3H, C_1-C_3-alkyl, C_1-C_3-alkoxy; and

R^{51} and R^{52} independently or –H or C_1-C_3-alkyl.

[0007] Z^1 is preferably a monocyclic 5-7 membered heterocyclyl or a 5-6 membered heteroaryl. In particularly preferred embodiments Z^1 is morpholinyl, thiazolyl, oxadiazolyl, tetrahydropyranyl, or oxazepanyl.

[0008] Y^1 is preferably -H, dimethylaminomethyl, (4-methylpiperizin-1-yl)methyl, piperidinyl, 1-methylpiperidin-4-yl, morpholin-4-ylmethyl, or phenylmethyl.

[0009] Preferably n1 is 1.

[0010] X^2 is preferably -NH-.

[0011] R^2 is preferably $-CH_3$.

[0012] n2 is preferably 0.

[0013] Ar is preferably phenyl optionally substituted with 1 or 2 R^{50} substituents. More preferably, Ar is dichlorophenyl.

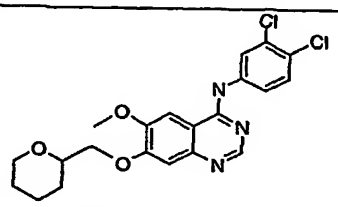
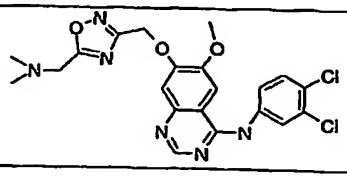
[0014] In another preferred embodiment, the invention comprises compounds according to any one of paragraphs [0006], [0009], [0009], [0011], [0012], or [0013] wherein:

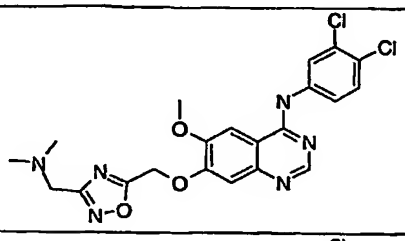
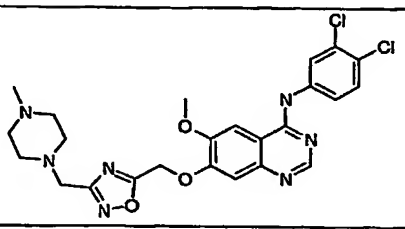
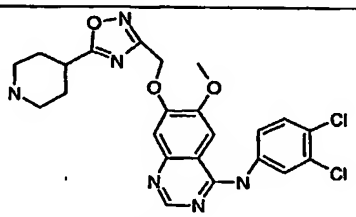
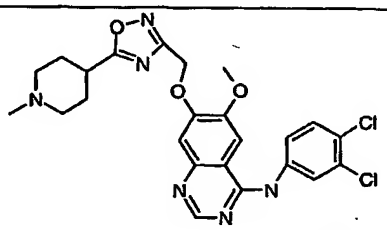
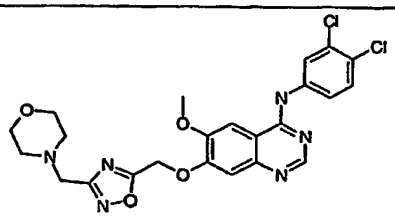
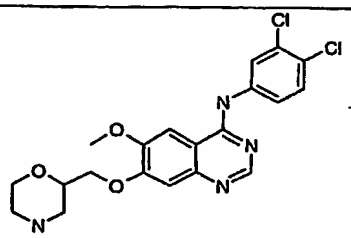
X^1 is a substituted, 3-7 membered, saturated carbocyclyl or heterocyclyl with 1 or 2 annular heteroatoms, wherein the ring is optionally substituted with C_1-C_3-alkyl, C_1-C_3- alkoxy, C_1-C_3-hydroxyalkyl, $(R^{10})(R^{11})N(CH_2)_{n4}$-, $(R^{10})(R^{11})N$-, or hydroxy, provided there are no geminal heteroatom substitutions or N-O bonds; and

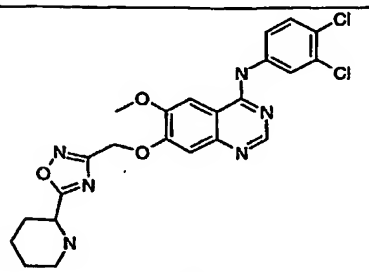
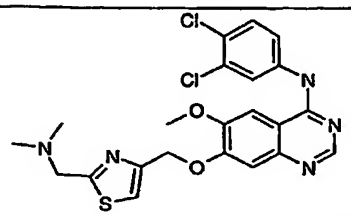
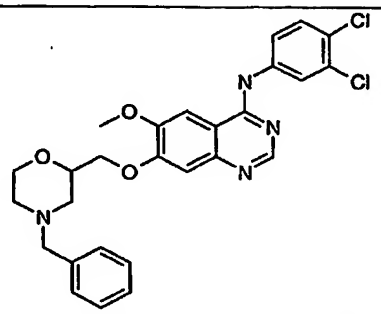
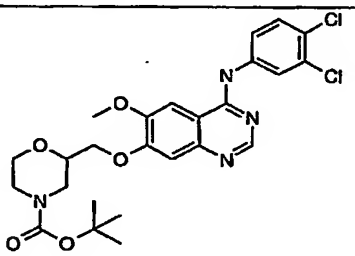
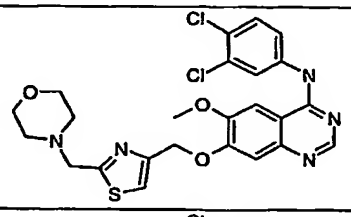
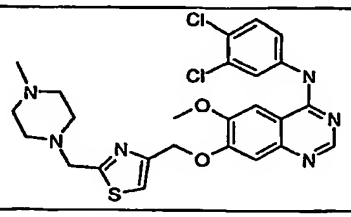
R^{10}, and R^{11} are independently C_1-C_3-alkyl.

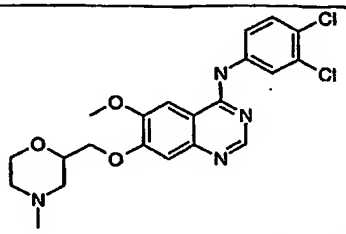
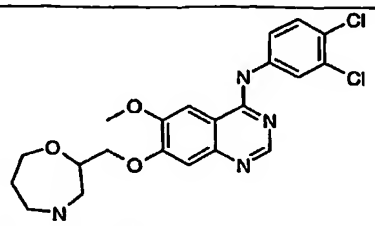
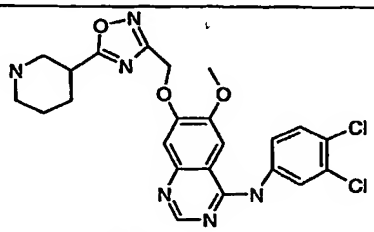
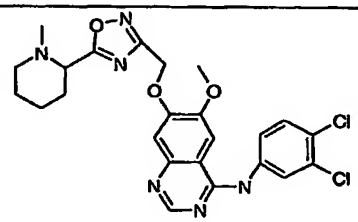
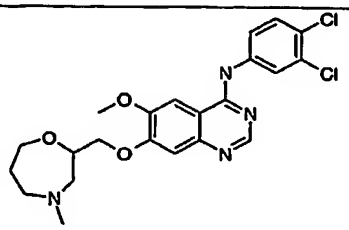
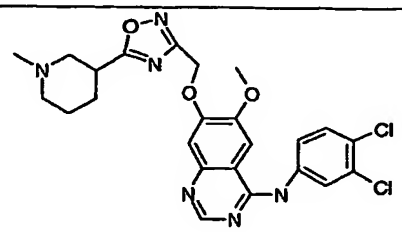
[0015] In a preferred embodiment of paragraph [0006], the compound is selected from those listed in Table 1:

Table 1

Structure	EphB4 activity (nM)	Name
	35.4	N-(3,4-dichlorophenyl)-6-(methyloxy)-7-[(tetrahydro-2H-pyran-2-ylmethyl)oxy]quinazolin-4-amine
	36.6	N-(3,4-dichlorophenyl)-7-[({5-[(dimethylamino)methyl]-1,2,4-oxadiazol-3-yl}methyl)oxy]-6-(methyloxy)quinazolin-4-amine

Structure	EphB4 activity (nM)	Name
	125.8	N-(3,4-dichlorophenyl)-7-[({3-[(dimethylamino)methyl]-1,2,4-oxadiazol-5-yl}methyl)oxy]-6-(methyloxy)quinazolin-4-amine
	88.8	N-(3,4-dichlorophenyl)-6-(methyloxy)-7-[({3-[(4-methylpiperazin-1-yl)methyl]-1,2,4-oxadiazol-5-yl}methyl)oxy]quinazolin-4-amine
	49.9	N-(3,4-dichlorophenyl)-6-(methyloxy)-7-{[(5-piperidin-4-yl-1,2,4-oxadiazol-3-yl)methyl]oxy}quinazolin-4-amine
	34.3	N-(3,4-dichlorophenyl)-6-(methyloxy)-7-({[5-(1-methylpiperidin-4-yl)-1,2,4-oxadiazol-3-yl]methyl}oxy)quinazolin-4-amine
	57.3	N-(3,4-dichlorophenyl)-6-(methyloxy)-7-({[3-(morpholin-4-ylmethyl)-1,2,4-oxadiazol-5-yl]methyl}oxy)quinazolin-4-amine
	19.3	N-(3,4-dichlorophenyl)-6-(methyloxy)-7-[(morpholin-2-ylmethyl)oxy]quinazolin-4-amine

Structure	EphB4 activity (nM)	Name
	22.6	N-(3,4-dichlorophenyl)-6-(methyloxy)-7-{[(5-piperidin-2-yl-1,2,4-oxadiazol-3-yl)methyl]oxy}quinazolin-4-amine
	126.7	N-(3,4-dichlorophenyl)-7-[({2-[(dimethylamino)methyl]-1,3-thiazol-4-yl}methyl)oxy]-6-(methyloxy)quinazolin-4-amine
	72.4	N-(3,4-dichlorophenyl)-6-(methyloxy)-7-({[4-(phenylmethyl)morpholin-2-yl]methyl}oxy)quinazolin-4-amine
	70.5	1,1-dimethylethyl 2-({[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)morpholine-4-carboxylate
	60.7	N-(3,4-dichlorophenyl)-6-(methyloxy)-7-({[2-(morpholin-4-ylmethyl)-1,3-thiazol-4-yl]methyl}oxy)quinazolin-4-amine
	34.6	N-(3,4-dichlorophenyl)-6-(methyloxy)-7-[({2-[(4-methylpiperazin-1-yl)methyl]-1,3-thiazol-4-yl}methyl)oxy]quinazolin-4-amine

Structure	EphB4 activity (nM)	Name
	12.6	N-(3,4-dichlorophenyl)-7-{[(4-methylmorpholin-2-yl)methyl]oxy}-6-(methyloxy)quinazolin-4-amine
	15.5	N-(3,4-dichlorophenyl)-6-(methyloxy)-7-[(1,4-oxazepan-2-ylmethyl)oxy]quinazolin-4-amine
	19.4	N-(3,4-dichlorophenyl)-6-(methyloxy)-7-{[(5-piperidin-3-yl-1,2,4-oxadiazol-3-yl)methyl]oxy}quinazolin-4-amine
	27	N-(3,4-dichlorophenyl)-6-(methyloxy)-7-({[5-(1-methylpiperidin-2-yl)-1,2,4-oxadiazol-3-yl]methyl}oxy)quinazolin-4-amine
	3.2	N-(3,4-dichlorophenyl)-7-{[(4-methyl-1,4-oxazepan-2-yl)methyl]oxy}-6-(methyloxy)quinazolin-4-amine
	18.4	N-(3,4-dichlorophenyl)-6-(methyloxy)-7-({[5-(1-methylpiperidin-3-yl)-1,2,4-oxadiazol-3-yl]methyl}oxy)quinazolin-4-amine

[0016] The compounds of the invention are ephrin receptor inhibitors and, therefore, are useful as laboratory tools for studying the role of ephrin receptors in biological processes *in vitro* and *in vivo*. The compounds of the invention are also useful for treating diseases mediated by ephrin receptors, including tumor growth and angiogenesis.

[0017] The compounds of the invention can be made using protocols and techniques both known and routine to those skilled in the art.

[0018] Unless expressly stated to the contrary, the following definitions apply uniformly throughout. For simplicity, moiety names are expressed as univalent chemical moieties (*e.g.*, alkyl, aryl, etc.). Nevertheless, such terms are also used to convey corresponding multivalent moieties (eg alkylene, arylene, etc.) under the proper structural circumstances. All atoms are understood to have their normal number of valences for bond formation (*i.e.*, 4 for carbon, 3 for N, 2 for O, and 2, 4, or 6 for S, depending on the oxidation state of the S). Also, to the extent that a compound or moiety exists in multiple tautomeric forms, all forms are intended to be encompassed.

[0019] The term alkyl refers to a univalent C_1 to C_6 saturated straight, branched, or cyclic alkane moiety and specifically includes methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, cyclopentyl, isopentyl, neopentyl, hexyl, isohexyl, cyclohexyl, 3-methylpentyl, 2,2-dimethylbutyl, and 2,3-dimethylbutyl. The alkyl group is optionally substituted with any appropriate group, including but not limited to one or more moieties selected from the group consisting of halo, hydroxyl, amino, alkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphate, or phosphonate, either unprotected, or protected as necessary, as known to those skilled in the art or as taught, for example, in Greene, *et al.*, "Protective Groups in Organic Synthesis," John Wiley and Sons, Third Edition, 1999.

[0020] The term alkoxy refers to an alkyl moiety having a terminal –O- with a free valence, *e.g.*, CH_3CH_2-O-;

[0021] The term alkenyl refers to a univalent C_2-C_6 straight, branched, or in the case of C_{5-6}, cyclic hydrocarbon with at least one double bond.

[0022] The term alkynyl refers to a univalent C_2-C_6 straight, branched, or in the case of C_{5-6}, cyclic hydrocarbon with at least one triple bond.

[0023] The term hydrocarbyl refers to a saturated, mono- or poly-unsaturated straight, branched or cyclic hydrocarbon (*i.e.*, alkyl, alkenyl, and alkynl) and specifically includes methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, cyclopentyl, isopentyl, neopentyl, hexyl, isohexyl, cyclohexyl,

3-methylpentyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, acetylenyl, propynyl, and -C≡C-CH_2(alkyl) (including -C≡C-$CH_2(CH_3)$.

[0024] A carbocyclyl moiety is a cyclic hydrocarbyl.

[0025] The term aryl refers to a univalent phenyl (preferably), biphenyl, or naphthyl. The aryl group can be optionally substituted with any suitable group, including but not limited to one or more moieties selected from the group consisting of halo, hydroxyl, amino, alkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphate, or phosphonate, either unprotected, or protected as necessary, as known to those skilled in the art, for example, as taught in Greene, et al., "Protective Groups in Organic Synthesis," John Wiley and Sons, Third Edition, 1999).

[0026] The term heteroatom means O, S, or N.

[0027] The term heterocyclyl refers to a cyclic alkyl or alkenyl moiety as defined above wherein one or more ring carbon atoms is replaced with a heteroatom. Specifically excluded from the scope of this term are compounds having adjacent annular O and/or S atoms

[0028] The term halo refers to chloro, fluoro, iodo, or bromo.

[0029] The term unsaturated or mono- or poly-unsaturated C_3-C_{14}-mono- or fused poly-cyclic hydrocarbyl optionally containing one, two, or three annular heteroatoms per ring refers to an aromatic or non-aromatic hydrocarbyl of 3 - 14 carbons forming a single ring or multiple fused rings and having one or more double and/or triple bonds and up to two heteroatoms as ring members of each ring. A non-exhaustive list of illustrative examples include cyclopentenyl, 2,4-cyclopentadienyl, phenyl, indenyl, naphthyl, 5,6,7,8-tetrahydro-2-naphthyl, phenanthryl, furyl, thienyl, pyranyl, isobenzofuranyl, chromenyl, pyrrolyl, imidazolyl, isoxazolyl, pyridyl, pyrazinyl, pyrimidinyl, oxadiazolyl, indolyl, quinolyl, carbazolyl, acrydinyl, furazanyl, etc. Specifically excluded from the scope of this term are compounds having adjacent annular O and/or S atoms.

[0030] A moiety that is substituted is one in which one or more hydrogens have been independently replaced with another chemical substituent. As a non-limiting example, substituted phenyls include 2-flurophenyl, 3,4-dichlorophenyl, 3-chloro-4-fluoro-phenyl, 2-fluor-3-propylphenyl. As another non-limiting example, substituted n-octyls include 2,4 dimethyl-5-ethyl-octyl and 3-cyclopentyl-octyl.

[0031] The term "pharmaceutically acceptable salts, esters, amides, and prodrugs" as used herein refers to those carboxylate salts, amino acid addition salts, esters, amides, and prodrugs of the compounds of the present invention which are, within the scope of sound medical judgment,

suitable for use in contact with the tissues of patients without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention. The term "salts" refers to the relatively non-toxic, inorganic and organic acid addition salts of compounds of the present invention. These salts can be prepared in situ during the final isolation and purification of the compounds or by separately reacting the purified compound in its free base form with a suitable organic or inorganic acid and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, nitrate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactobionate and laurylsulphonate salts, and the like. These may include cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium, and the like, as well as non-toxic ammonium, quaternary ammonium and amine cations including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. The compounds can also be administered as pharmaceutically acceptable quaternary salts known by those skilled in the art, which specifically include the quaternary ammonium salt of the formula -NR + Z-, wherein R is hydrogen, alkyl, or benzyl, and Z is a counterion, including chloride, bromide, iodide, -O-alkyl, toluenesulfonate, methylsulfonate, sulfonate, phosphate, or carboxylate (such as benzoate, succinate, acetate, glycolate, maleate, malate, citrate, tartrate, ascorbate, benzoate, cinnamoate, mandeloate, benzyloate, and diphenylacetate). (See, for example, S. M. Berge, et al., "Pharmaceutical Salts," J. Pharm. Sci., 1977;66:1-19 which is incorporated herein by reference.)

[0032] Examples of pharmaceutically acceptable, non-toxic esters of the compounds of this invention include C_1 -C_6 alkyl esters wherein the alkyl group is a straight or branched chain. Acceptable esters also include C_5 -C_7 cycloalkyl esters as well as arylalkyl esters such as, but not limited to benzyl, C_1 -C_4 alkyl esters are preferred. Esters of the compounds of the present invention may be prepared according to conventional methods.

[0033] Examples of pharmaceutically acceptable, non-toxic amides of the compounds of this invention include amides derived from ammonia, primary C_1 -C_6 alkyl amines and secondary C_1 -C_6 dialkyl amines wherein the alkyl groups are straight or branched chain. In the case of secondary amines the amine may also be in the form of a 5- or 6-membered heterocycle containing one

nitrogen atom. Amides derived from ammonia, C_1 -C_3 alkyl primary amines, and C_1 -C_2 dialkyl secondary amines are preferred. Amides of the compounds of the invention may be prepared according to conventional methods.

[0034] The term "prodrug" refers to compounds that are rapidly transformed in vivo to yield the parent compound of the above formulae, for example, by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.

[0035] In addition, the compounds of the present invention can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the present invention.

[0036] The compounds of the present invention may also exist in different stereoisomeric forms by virtue of the presence of one or more asymmetric centers in the compound. The present invention contemplates all stereoisomeric forms of the compounds as well as mixtures thereof, including racemic mixtures. Individual stereoisomers may be obtained, if desired by methods known in the art as, for example, the separation of stereoisomers in chiral chromatographic columns.

[0037] In another embodiment, the invention comprises a pharmaceutical composition comprising a compound as described in any of paragraphs [0006]–[0015] and a pharmaceutically acceptable carrier.

[0038] The active compound is included in the pharmaceutically acceptable carrier or diluent in an amount sufficient to deliver to a patient a therapeutically effective amount without causing serious toxic effects in the patient treated. A preferred dose of the active compound for all of the above-mentioned conditions is in the range from about 0.01 to 300 mg/kg, preferably 0.1 to 100 mg/kg per day, more generally 0.5 to about 25 mg per kilogram body weight of the recipient per day. A typical topical dosage will range from 0.01–3% wt/wt in a suitable carrier. The effective dosage range of the pharmaceutically acceptable derivatives can be calculated based on the weight of the parent compound to be delivered. If the derivative exhibits activity in itself, the effective dosage can be estimated as above using the weight of the derivative, or by other means known to those skilled in the art.

[0039] The methods of the invention comprise administration to a mammal (preferably human) suffering from forms of cancer, arthritis, and diseases related to angiogenesis in which ephrin plays a critical role a pharmaceutical composition according to the invention in an amount sufficient to alleviate the condition. The compound is conveniently administered in any suitable unit dosage form, including but not limited to one containing 1 to 3000 mg, preferably 5 to 500 mg of active ingredient per unit dosage form. A oral dosage of 1–500, preferably 10-250, more preferably 25-250 mg is usually convenient.

[0040] The active ingredient should be administered to achieve peak plasma concentrations of the active compound of about 0.001–30 μM, preferably about 0.01–10 μM. This may be achieved, for example, by the intravenous injection of a solution or formulation of the active ingredient, optionally in saline, or an aqueous medium or administered as a bolus of the active ingredient.

[0041] The concentration of active compound in the drug composition will depend on absorption, distribution, inactivation, and excretion rates of the drug as well as other factors known to those of skill in the art. It is to be noted that dosage values will also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed composition. The active ingredient may be administered at once, or may be divided into a number of smaller doses to be administered at varying intervals of time.

[0042] Oral compositions will generally include an inert diluent or an edible carrier. They may be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition.

[0043] The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a dispersing agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterores; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring. When the dosage unit form is a capsule, it can

contain, in addition to material of the above type, a liquid carrier such as a fatty oil. In addition, dosage unit forms can contain various other materials which modify the physical form of the dosage unit, for example, coatings of sugar, shellac, or enteric agents. *See generally* "Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, PA.

[0044] The active compound or pharmaceutically acceptable salt or derivative thereof can be administered as a component of an elixir, suspension, syrup, wafer, chewing gum or the like. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors.

[0045] The active compound or pharmaceutically acceptable derivatives or salts thereof can also be mixed with other active materials that do not impair the desired action, or with materials that supplement the desired action, such as antibiotics, antifungals, other anti-inflammatories, or antiviral compounds.

[0046] Solutions or suspensions used for parenteral, intradermal, subcutaneous, or topical application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerin, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parental preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

[0047] If administered intravenously, preferred carriers are physiological saline or phosphate buffered saline (PBS).

[0048] In one embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation (CA) and Gilford Pharmaceuticals (Baltimore, Md.). Liposomal suspensions may also be pharmaceutically acceptable carriers. These may be prepared according to methods known to those skilled in the art, for example, as described in U.S. Pat. No. 4,522,811 (which is incorporated herein

by reference in its entirety). For example, liposome formulations may be prepared by dissolving appropriate lipid(s) (such as stearoyl phosphatidyl ethanolamine, stearoyl phosphatidylcholine, arachadoyl phosphatidylcholine, and cholesterol) in an inorganic solvent that is then evaporated, leaving behind a thin film of dried lipid on the surface of the container. An aqueous solution of the active compound or its monophosphate, diphosphate, and/or triphosphate derivatives are then introduced into the container. The container is then swirled by hand to free lipid material from the sides of the container and to disperse lipid aggregates, thereby forming the liposomal suspension.

[0049] The following examples are provided for illustrative purposes only and are not intended, nor should they be construed, as limiting in any manner. All patents and other publications recited herein are incorporated by reference in their entirety. In the case of any inconsistency between the express disclosures herein and those of the cited patents and/or publications, the express disclosures herein shall prevail.

EXAMPLES

Example 1

In vitro assays

Assay 1 (EphA2)

[0050] 384-well plates are coated with 2μg/well poly(glutamine-tyrosine) peptide in Tris Buffered Saline overnight at room temperature. The coating solution is removed and each well is blocked with 0.3% Bovine Serum Albumin for 1 hour at room temperature, the wells are aspirated and washed twice with Assay Buffer (20mM Tris pH 8.0, 10mM $MgCl_2$, 0.04% CHAPS. EphA2 (5nM final concentration) and test compounds, in a ten point dilution series, are added to the plate and the reaction is initiated by addition of γ-[33P]-ATP (3.3μCi/nmol) to a final concentration of 5μM. Following incubation at room temperature for 2 hours, the wells are aspirated and washed 9 times with 80μl/well phosphate buffered saline containing 0.2% Tween-20. Scintillation fluid (50μl/well) is added, the plates are sealed and activity assessed by liquid scintillation spectrometry.

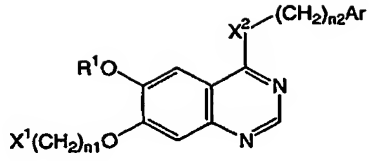
Assay 2 (EphB4)

[0051] 384-well plates were coated with 2μg/well poly(alanine-glutamine-lysine-tyrosine) peptide in 50mM sodium carbonate buffer, pH 9.6 containing 150mM NaCl and 3mM NaN_3 overnight at room temperature. The coating solution was removed and each well blocked with 0.3% Bovine Serum Albumin for 1 hour at room temperature, the wells were aspirated and washed twice with Assay

Buffer (20mM Tris pH 7.5, 10mM $MgCl_2$, 0.01% Triton-X-100, 100μM sodium orthovanadate. EphB4 (8nM final concentration) and test compounds, in a ten point dilution series, were added to the plate and the reaction was initiated by addition of γ-[33P]-ATP (3.3μCi/nmol) to a final concentration of 5μM. Following incubation at room temperature for 2.5 hours, the wells were aspirated and washed 6 times with 80μl/well phosphate buffered saline containing 0.2% Tween-20. Scintillation fluid (50μl/well) was added, the plates were sealed and activity assessed by liquid scintillation spectrometry. The results are presented above in Table 1.

We Claim:

1. A compound of structural formula I:



I

and pharmaceutically acceptable salts, esters, amides, and prodrugs thereof wherein

X^1 is Y^1-Z^1-;

Z^1 is an unsaturated or mono- or poly-unsaturated C_3-C_{14}-mono- or fused poly-cyclic hydrocarbyl optionally containing one, two, or three annular heteroatoms per ring and optionally substituted with from 1 to 3 R^{50} substituents;

Y^1 is -H, C_1-C_6-alkyl-L^2-L^1- optionally substituted by R^{50}, $X^3(CH_2)_{n3}$-, or $R^2R^3N(CH_2)_{n4}$-

X^3 is a saturated 5-7 membered heterocyclyl containing one or two annular heteroatoms and optionally substituted with from 1 to 3 R^{50} substituents;

L^1 is -CO-, or -SO_2-;

L^2 is a direct bond, -O-, or -NH-;

n1, n3, and n4 are independently 0, 1, 2, or 3;

R^2 and R^3 are independently C_1-C_3-alkyl optionally substituted with from 1 to 3 R^{50} substituents;

R^1 is C_1-C_3-alkyl optionally substituted with from 1 to 3 R^{50} substituents;

X^2 is -O-, -S-, or –NH-;

Ar is aryl with 1 to 3 ring substituents selected independently from Me-, -F, -Cl, -Br, -OH, -OMe;

n2 is 0 or 1;

R^{50} is halo, -OH, -$NR^{51}R^{52}$, -SH, -CO_2H, -CN, -NO_2, -SO_3H, C_1-C_3-alkyl, C_1-C_3-alkoxy; and

R^{51} and R^{52} independently or –H or C_1-C_3-alkyl.

2. The compound according to claim 1, wherein Z^1 is a monocyclic 5-7 membered heterocyclyl or a 5-6 membered heteroaryl.

3. The compound according to claim 2, wherein Z^1 is morpholinyl, thiazolyl, oxadiazolyl, tetrahydropyranyl, or oxazepanyl.

4. The compound according to any one of claims 1–3, wherein Y^1 is -H, dimethylaminomethyl, (4-methylpiperizin-1-yl)methyl, piperidinyl, 1-methylpiperidin-4-yl, morpholin-4-ylmethyl, or phenylmethyl.

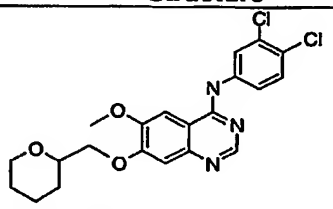
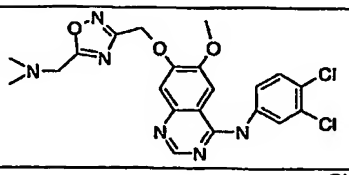
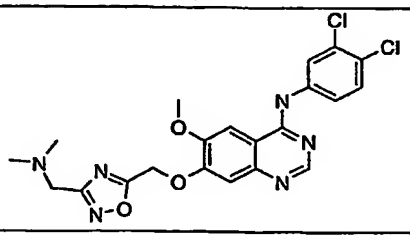
5. The compound according to claim 1 wherein X^2 is -NH-.

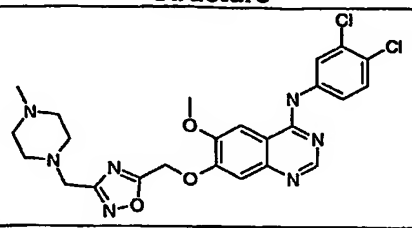
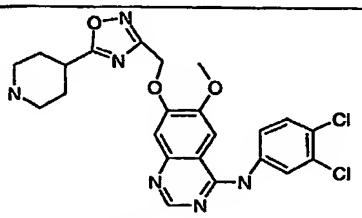
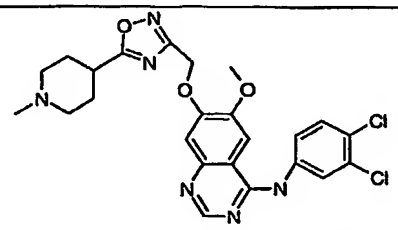
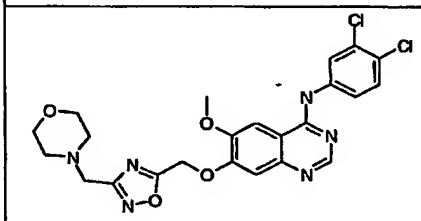
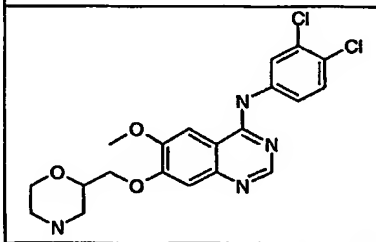
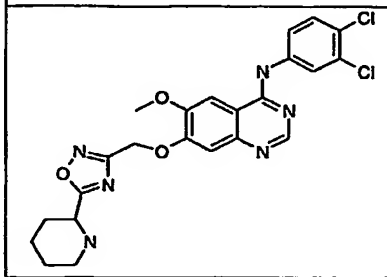
6. The compound according to claim 1 wherein Ar is phenyl optionally substituted with 1 or 2 R^{50} substituents.

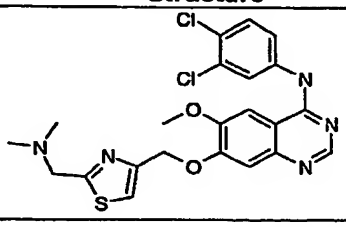
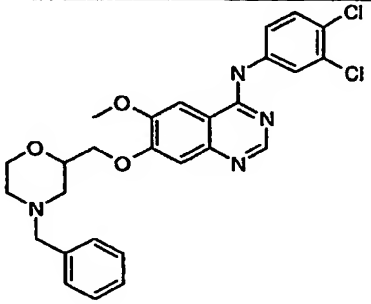
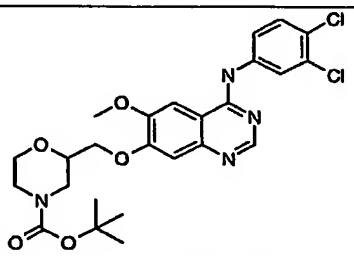
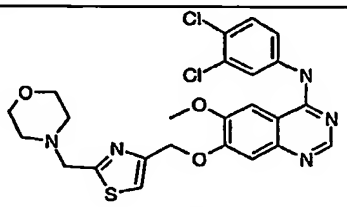
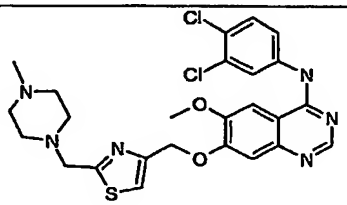
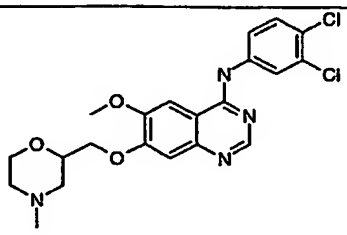
7. The compound according to claim 7 wherein Ar is dichlorophenyl.

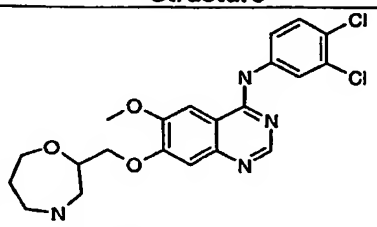
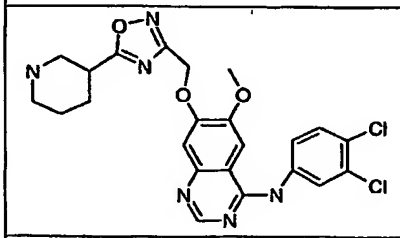
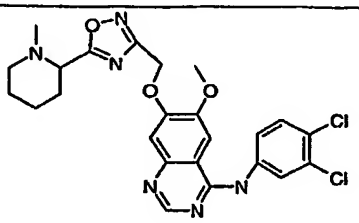
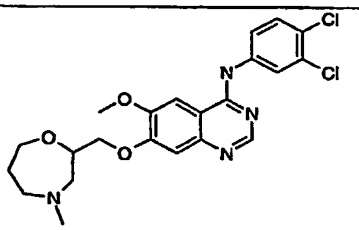
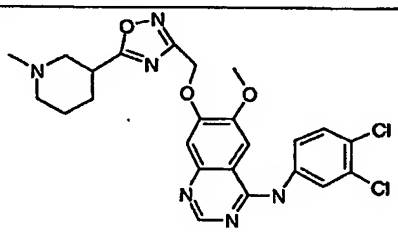
8. The compound according to any one of claims 1–3 wherein:
   n1 is 1;
   X^2 is -NH-;
   R^2 is $-CH_3$;
   n2 is 0; and
   Ar is phenyl optionally substituted with 1 or 2 R^{50} substituents.

9. The compound according to claim 1 selected from the compounds in the following table:

Structure	Name
	N-(3,4-dichlorophenyl)-6-(methyloxy)-7-[(tetrahydro-2H-pyran-2-ylmethyl)oxy]quinazolin-4-amine
	N-(3,4-dichlorophenyl)-7-[({5-[(dimethylamino)methyl]-1,2,4-oxadiazol-3-yl}methyl)oxy]-6-(methyloxy)quinazolin-4-amine
	N-(3,4-dichlorophenyl)-7-[({3-[(dimethylamino)methyl]-1,2,4-oxadiazol-5-yl}methyl)oxy]-6-(methyloxy)quinazolin-4-amine

Structure	Name
	N-(3,4-dichlorophenyl)-6-(methyloxy)-7-[({3-[(4-methylpiperazin-1-yl)methyl]-1,2,4-oxadiazol-5-yl}methyl)oxy]quinazolin-4-amine
	N-(3,4-dichlorophenyl)-6-(methyloxy)-7-{[(5-piperidin-4-yl-1,2,4-oxadiazol-3-yl)methyl]oxy}quinazolin-4-amine
	N-(3,4-dichlorophenyl)-6-(methyloxy)-7-({[5-(1-methylpiperidin-4-yl)-1,2,4-oxadiazol-3-yl]methyl}oxy)quinazolin-4-amine
	N-(3,4-dichlorophenyl)-6-(methyloxy)-7-({[3-(morpholin-4-ylmethyl)-1,2,4-oxadiazol-5-yl]methyl}oxy)quinazolin-4-amine
	N-(3,4-dichlorophenyl)-6-(methyloxy)-7-[(morpholin-2-ylmethyl)oxy]quinazolin-4-amine
	N-(3,4-dichlorophenyl)-6-(methyloxy)-7-{[(5-piperidin-2-yl-1,2,4-oxadiazol-3-yl)methyl]oxy}quinazolin-4-amine

Structure	Name
	N-(3,4-dichlorophenyl)-7-[({2-[(dimethylamino)methyl]-1,3-thiazol-4-yl}methyl)oxy]-6-(methyloxy)quinazolin-4-amine
	N-(3,4-dichlorophenyl)-6-(methyloxy)-7-({[4-(phenylmethyl)morpholin-2-yl]methyl}oxy)quinazolin-4-amine
	1,1-dimethylethyl 2-({[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)morpholine-4-carboxylate
	N-(3,4-dichlorophenyl)-6-(methyloxy)-7-({[2-(morpholin-4-ylmethyl)-1,3-thiazol-4-yl]methyl}oxy)quinazolin-4-amine
	N-(3,4-dichlorophenyl)-6-(methyloxy)-7-[({2-[(4-methylpiperazin-1-yl)methyl]-1,3-thiazol-4-yl}methyl)oxy]quinazolin-4-amine
	N-(3,4-dichlorophenyl)-7-{[(4-methylmorpholin-2-yl)methyl]oxy}-6-(methyloxy)quinazolin-4-amine

Structure	Name
	N-(3,4-dichlorophenyl)-6-(methyloxy)-7-[(1,4-oxazepan-2-ylmethyl)oxy]quinazolin-4-amine
	N-(3,4-dichlorophenyl)-6-(methyloxy)-7-{[(5-piperidin-3-yl-1,2,4-oxadiazol-3-yl)methyl]oxy}quinazolin-4-amine
	N-(3,4-dichlorophenyl)-6-(methyloxy)-7-({[5-(1-methylpiperidin-2-yl)-1,2,4-oxadiazol-3-yl]methyl}oxy)quinazolin-4-amine
	N-(3,4-dichlorophenyl)-7-{[(4-methyl-1,4-oxazepan-2-yl)methyl]oxy}-6-(methyloxy)quinazolin-4-amine
	N-(3,4-dichlorophenyl)-6-(methyloxy)-7-({[5-(1-methylpiperidin-3-yl)-1,2,4-oxadiazol-3-yl]methyl}oxy)quinazolin-4-amine

10. A composition comprising a compound according to any one of claims 1–9 and a pharmaceutically acceptable carrier.

11. A method of inhibiting an ephrin receptor *in vivo*, the method comprising administering to a subject an effective amount of a composition according to claim 10.

ABSTRACT OF THE DISCLOSURE

The present invention comprises quinazoline-based compounds that are ephrin inhibitors, pharmaceutical compositions comprising the compounds, and methods of using the compounds and compositions to inhibit ephrin receptors and treat diseases mediated by ephrin receptors, including diseases associated with abnormal cell proliferation (*e.g.*, tumors) and angiogenesis.